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Masman, Marcelo F.; Heberling, Matthew M.; Janssen, Dick B.

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fundamental understanding of protein-protein interactions, but also to the development of efficient computational methods to rationally design protein interfaces with tunable specificity and affinity, and numerous applications in biomedicine.

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### 3310-Pos Board B38

#### From Aminomutases to Ammonia Lyases: A Protein Engineering Study

Marcelo F. Masman, Matthew M. Heberling, Dick B. Janssen.

Biotransformation and Biocatalysis, University of Groningen, Groningen, Netherlands.

Ammonia lyases and aminomutases are emerging as important enzymatic systems, not only in green synthetic routes to chiral amines, but also as potential target for enzyme therapeutic for treating diseases such as phenylketonuria and cancer (1). On the other hand,  $\beta$ -amino acids harbor many applications in their free form and as building blocks of bioactive compounds (2, 3). Although, these eco-friendly biocatalytic routes have been extensively explored, they are far from optimal. The aim of this work is to engineer a phenylalanine aminomutase (PAM) to acquire lyase properties for the efficient production of enantio-pure  $\beta$ -Phe (key component of taxol (2)). Thus, this study was guided by molecular modeling techniques to decipher which structural components functionally separate PAM and the phenylalanine ammonia lyase (PAL). Despite the great structural similarity of the active site of these enzymes, PAL is  $\alpha$ -selective with much faster deamination rates relative to PAM, which exhibits 50%  $\alpha$ - and  $\beta$ -regioselectivity (1, 4). Recent studies have implicated loop regions as key structural determinants between PAM and PAL (5). Here, we report novel insight into the implications of the active-site loop residues of PAM, which influence mutase/lyase activity. Several mutants were proposed, cloned, expressed and characterized. Overall, this enzyme engineering work represents the first successful attempt to convert a PAM to a PAL through strict mutase-to-lyase residue mutations. Such a breakthrough may guide future investigations into the functional determinants of these enzymes and possibly foster the engineering of faster PAM variants used for the efficient synthesis of  $\beta$ -Phe.

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### 3311-Pos Board B39

#### Simple Rules Imposed on a Primitive Cubic Lattice Robustly Generate Structures that Mimic Features of Real Proteins

Deniz Turgut<sup>1</sup>, Osman B. Okan<sup>1</sup>, Aravind Rammohan<sup>2</sup>, Angel E. Garcia<sup>1</sup>, Rahmi Ozisik<sup>1</sup>.

<sup>1</sup>Materials Science and Engineering, Rensselaer Polytechnic Institute, Troy, NY, USA, <sup>2</sup>Corning Inc., Painted Post, NY, USA.

We introduce a set of simple and well-defined rules, which produce protein-like networks when they are imposed on a primitive cubic lattice. The resulting artificial structures successfully mimic the geometric and topological features of real proteins, and therefore, provide the opportunity to understand characteristics of protein structures and lead to the creation of synthetic proteins. The proposed method does not involve a chain-fitting step and does not require individual set of reference structures. We start with a cubic lattice, whose lattice sites contain beads representing protein residues. Many cubic lattices are emptied up to 60% vacancy concentration by randomly removing beads while maintaining a connected network of occupied sites. The maximum vacancy concentration of 60% was obtained from first and second nearest neighbor occupancies of real protein residues. A Reverse Monte-Carlo/Simulated Annealing (RMC/SA) simulation that is constrained to fit the average radial distribution function of residues of 278 proteins is then performed. Results indicate that the RMC/SA procedure recovers the average radial distribution function without disturbing other structural properties such as bond orientational order parameters and network topology. Based on various structural properties, our results indicate that these artificially created structures closely resemble real residue networks.

### 3312-Pos Board B40

#### Inferring Protein Structures from Sparse and Ambiguous Data

Justin L. MacCallum, Alberto Perez, Kenneth A. Dill.

Laufer Center for Physical and Quantitative Biology, Stony Brook, Stony Brook, NY, USA.

We have developed a new computational framework called MeLD: Modeling with Limited Data. MeLD is an integrative modeling approach that combines physical modeling and statistical mechanics with data from experiment and

bioinformatics. The approach is tailored to deal with data with the following properties: (1) the data is sparse, where there may be little to no information about some part of the structure; (2) the information is often ambiguous and not totally reliable. I will present several applications of MeLD, including successful structure determination from sparsely-labeled NMR data and EPR data, accurate structures predicted from evolutionarily inferred contacts, and the correct prediction of the binding mode of an intrinsically disordered protein based on site-directed mutagenesis data.

### 3313-Pos Board B41

#### Simulation Study of Soluble Toxic Oligomeric Structures of Amyloid-Beta

Sukanya Sasmal<sup>1</sup>, Timothy Balmore<sup>2</sup>, K. Aurelia Ball<sup>3</sup>, Teresa Head-Gordon<sup>4</sup>.  
<sup>1</sup>Department of Chemical and Biomolecular Engineering, University of California, Berkeley, Berkeley, CA, USA, <sup>2</sup>Chemical Biology, University of California, Berkeley, Berkeley, CA, USA, <sup>3</sup>Graduate Group in Biophysics, University of California, Berkeley, Berkeley, CA, USA, <sup>4</sup>Department of Chemistry, Bioengineering and Chemical and Biomolecular Engineering, University of California, Berkeley, Berkeley, CA, USA.

Although early attention has focused on toxicity of amyloid plaques as the cause of Alzheimer's disease (AD), there is stronger evidence that soluble A $\beta$  oligomers, and more recently pre-fibrillar oligomers, show better correlation with AD symptoms than do the insoluble fibrillar states exhibited at the completion of the amyloid cascade. In recent work a new oligomeric A $\beta$  form known as the "globulomer" was found to inhibit calcium uptake by neuronal cells and to contribute to memory loss in lab animals. At present we have no knowledge of the globulomer structure, nor a smaller species known as the pre-globulomer, which is usually a necessary first step in the design of small molecule drug therapeutics. We will present our hypothesis about the structural ensembles of these two oligomeric forms based on molecular dynamics simulations and calculation of NMR observables and amide exchange data.

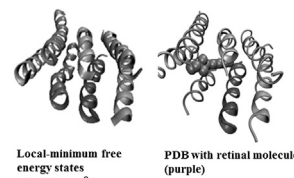
### 3314-Pos Board B42

#### Computer Simulations for Predicting Membrane Protein Structures with the Replica-Exchange Methods and Implicit Membrane Model of a Restricted Configurational Space

Ryo Urano, Yuko Okamoto.

Nagoya University, Nagoya, Aichi, Japan.

The structures of membrane proteins are necessary to examine the functions and the mechanisms. The determination of membrane proteins takes a long time yet despite the development of experimental techniques. Thus, we have developed simulation methods for predicting alpha-helical membrane proteins. For the purpose, replica-exchange methods (REM) and a particular implicit membrane model are used. Distortions and kinked helix structures in transmembrane helices are frequently observed as a characteristic appearance of experimental membrane protein structures. Concerted rotation of torsion angles and dihedral angle of main chains in Monte Carlo move sets are implemented for including the distortions. Our implicit membrane model is to mimic the sampled configuration during native folding of membrane proteins after inserted membrane environment. We applied this method to bacteriorhodopsin, which has seven distorted transmembrane helices. From the random ideal helix configuration, we obtained local-minimum free energy states by REM simulations and principal component analysis. The RMSD value of whole backbone atoms from the PDB structure is 2.5 angstroms. The RMSD values in each helix structure about distortions are also less than about 1.5 angstroms.



### 3315-Pos Board B43

#### Toward a Global View of the Conformational Landscape of the Human Kinome

Daniel L. Parton<sup>1</sup>, Diwakar Shukla<sup>2</sup>, Yutong Zhao<sup>2</sup>, Vijay S. Pande<sup>2</sup>, John D. Chodera<sup>1</sup>.

<sup>1</sup>Memorial Sloan-Kettering Cancer Center, New York, NY, USA, <sup>2</sup>Stanford University, Stanford, CA, USA.

The human genome contains about 500 protein kinases, which play a central role in the regulation of the majority of cellular pathways. Mutations in kinase genes - often resulting in dysregulation of their phosphotransferase activity - are a frequent cause of disease, including many types of cancer. Kinases are especially flexible proteins, and undergo significant conformational changes during their catalytic and regulatory cycles. This conformational heterogeneity is also of fundamental importance in determining the binding affinity and